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Dated 26 MAY 2000

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P01/7700 0.00-0002762.3

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — PHM.70654/GB/P

2. Patent application number *(The Patent Office will fill in this part)* — 08 FEB 2000 — 0002762.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca UK Limited
15 Stanhope Gate
LONDON
W1Y 6LN, GB

Patents ADP number *(if you know it)* 78102940001

6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — METHOD OF TREATMENT

5. Name of your agent *(if you have one)*

DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Global Intellectual Property, Patent
AstraZeneca UK Limited
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

Patents ADP number *(if you know it)* 78224710O

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

I[illegible]nts Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	4 DML
Claim(s)	
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Lynda M. Slack Date 8th Feb 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs Lynda M Slack 01625-516173

Warning

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

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METHOD OF TREATMENT

This invention relates to a method of controlling the weight of patients and is particularly concerned with a method of controlling weight in treating patients suffering from psychoses.

It is known that many drugs used to treat mental disorders in humans cause significant increases in body weight and Sussman et al., Psychiatric Annals 1999, 29(10) 580 state that with the possible exception of molidinone hydrochloride and loxapine, since their introduction into clinical practice, virtually all antipsychotic drugs, both conventional and atypical, have been associated with varying degrees of weight gain. Weight gain has been recognised as detrimental to patient acceptability of the drug, as detrimental to patient satisfaction and may give rise to other medical problems.

It is known that anti-psychotic agents such as clozapine and olanzapine tend to result in weight gain.

We have now unexpectedly found that 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine has properties which means that it is potentially useful in managing the weight of patients.

The compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine and its use in treating schizophrenia is described in granted European Patent No. EP 240,228.

The term "Agent" referred to hereinafter means 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine or a pharmaceutically acceptable salt thereof.

According to the present invention there is provided a method of managing the weight of a patient comprising administering an effective amount of the "Agent" thereof to said patient.

The present invention also provides the use of the "Agent" for the manufacture of a medicament for managing the weight of a patient.

The "Agent" is particularly effective in inducing weight loss in patients who have tended to gain weight when treated with other antipsychotics such as clozapine. Under such circumstances, the "Agent" may reverse at least part of any weight gained as a result of

treatment with the antipsychotic such as clozapine. The "Agent" is also effective in therapy wherein the "Agent" is the sole antipsychotic to be administered to the patient.

The "Agent" may be administered as the compound, 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine or may be administered in the form of a pharmaceutically acceptable salt. Examples of suitable salts include, for example, chloride, maleate, fumarate, citrate, phosphate, methane sulphonate and sulphate salts. Preferred salts include fumarates and a particularly preferred salt is the hemi-fumarate.

It is generally preferred that the "Agent" comprises the compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine in the form of a salt, and in particular a fumarate (2:1) salt.

In the treatment of the diseases mentioned above the "Agent" may be administered orally or parenterally in a conventional dosage form such as tablets, pills, capsules, injectables or the like. The dosage in mg/kg of body weight of the compound used to treat mammals will vary according to the size of the mammal and particularly with respect to the brain/body weight ratio. In general, a higher mg/kg dosage for a small animal such as a dog will have the same effect as a lower mg/kg dosage in an adult human. A minimum effective dosage for the "Agent" will be at least about 1.0 mg/kg of body weight per day for mammals with a maximum dosage for a small mammal such as a dog, of about 200 mg/kg per day.

For humans, a dosage of about 1.0 to 40 mg/kg per day will generally be effective.

Typically, a dosage of about 25mg to 800mg per day will generally be effective. Usually, a dosage of about 150mg to 750mg per day will be administered, with a convenient dosage being about 300mg per day. In some groups of patients a lower dosage may be preferred such as 100mg per day. The dosage can be given once daily or in divided doses, for example, 2 to 4 doses daily. The dose may be conventionally formulated in an oral or parenteral dosage form by compounding 25 to 500 mg per unit dosage of conventional vehicle, excipient, binder, preservative, stabiliser, flavour or the like as called for by accepted pharmaceutical practice, for example, as described in US Patent 3,755,340.

The "Agent" may be used in pharmaceutical compositions as the sole active ingredient or may be contained in a pharmaceutical composition together with one or more other active ingredients, or it may be co-administered with one or more known drugs.

The "Agent" may be administered in conjunction with one or more other agents useful for treating psychoses or related disorders.

As indicated above, where the "Agent" is administered in conjunction with another agent it may be administered simultaneously, sequentially or separately with that other agent or agents. Thus, as indicated above the "Agent" may be formulated with the other agent or agents or may be presented as a separate formulation.

The preparation of 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine and its pharmaceutically acceptable salts is described in, for example, granted European Patents Nos. EP 240,218; EP 282,236 and in pending International Patent Application No. PCT/GB98/02260. This compound is commercially available under the generic name quetiapine fumarate.

The invention will now be illustrated with reference to the following, non-limiting examples.

Example 1

427 patients (277 male; 150 female) were treated with quetiapine during controlled and open-label extension studies for up to 3.5 years and weight changes were monitored at specified time intervals throughout this period. The patients were in the age range 18-75 with a mean age of 37.3 years.

Patients were grouped using an observed cases approach within specified time intervals. Although patients received a variety of comparator antipsychotic agents during the controlled studies, they only received quetiapine during the open-label extension period. Data were obtained for 30% of patients for at least one year.

Over the first 4 weeks, a mean weight loss of 0.36 Kg (n=17) was recorded. At subsequent time intervals weight changes were -0.17 kg (n=49) at weeks 5-8; +1.58 kg (n=171) at weeks 9-13; +0.29 kg(n=153) at weeks 14-26; +1.73 kg (n=128) at weeks 27-39; -1.47 kg (n=37) at weeks 40-52; +2.00 kg (n=116) at weeks 53-78; +3.43 kg (n=64) at week 79-104; +3.45 kg (n=44) at weeks 105-130 and +0.36 kg (n=9) at weeks 131-156. Patients received a mean quetiapine dosage of approximately 475 mg/day at completion of the open-label trial. Only one patient withdrew from the open-label study due to an adverse event of weight gain.

Thus, an unexpected clinical effect of quetiapine is its apparent capability of being associated with minimal weight gain unlike olazapine and clozapine. Note: quetiapine is 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine fumarate (2:1) salt.

Example 2

The following illustrates representative pharmaceutical dosage forms containing the compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine fumarate (2:1).

(a) Tablet	mg/tablet
Quetiapine fumarate	50.0
Mannitol, USP.....	223.75
Croscarmellose sodium.....	6.0
Maize starch.....	15.0
Hydroxypropylmethylcellulose (HPMC),	2.25
Magnesium stearate.....	3.0

(b) Capsule	
Quetiapine fumarate.....	10.0
Mannitol, USP.....	488.5
Croscarmellose sodium.....	15.0
Magnesium stearate.....	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

A preferred formulation is that available commercially as quetiapine fumarate.